Mini-review

Hyperparathyroidism in multiple endocrine neoplasia type II A

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Summary

Primary hyperparathyroidism (PHPT) in multiple endocrine neoplasia (MEN) 2A occurs in only 15-30% of patients. It is rarely the first feature recognized in the syndrome, is generally mild and is sometimes expressed only as parathyroid tumors discovered during surgery for medullary thyroid carcinoma. A predisposition to MEN 2 is caused by germline mutations of the RET proto-oncogene on chromosome 10q11.2. Genetic studies have demonstrated the association of PHPT with a specific mutation at codon 634 (C634R). Therefore, all codon 634 mutation carriers are at some risk for hyperparathyroidism and should be submitted to an early screening of the disease. The rarity of MEN 2A-related PHPT has prevented the establishment of a well-defined therapeutic strategy for treating this condition, so that recommendations about the surgical approach have been controversial. Patients with MEN 2A should have annual screenings for hyperparathyroidism by serum calcium and intact parathyroid hormone level measurements. Parathyroidectomy should be considered in all patients who have some evidence of symptomatic disease. The objectives of parathyroid surgery are to a) obtain and maintain normocalcemia for the longest time possible, b) avoid iatrogenic hypoparathyroidism, and c) facilitate future surgery for recurrent disease. Finally, most of the patients with MEN 2A-related PHPT have mild disease and they could be classified as asymptomatic based on the NIH consensus conference regarding the diagnosis and management of asymptomatic PHPT. Therefore, these patients can be followed up safely without parathyroid surgery.

KEY WORDS: primary hyperparathyroidism, MEN 2A, RET proto-oncogene.

Introduction

Primary hyperparathyroidism (PHPT) in its hereditary variants represents only about 5% of all PHPT but it assumes several forms, has characteristic associations, and requires special management.
Among all syndromes of hereditary PHPT (multiple endocrine neoplasia type 1 and type 2A, familial hypocalciuric hypercalcemia, neonatal severe PHPT, hyperparathyroidism-jaw tumor syndrome, and familial isolated hyperparathyroidism) (Table I), MEN 2A is the only one in which PHPT is not the most common endocrine feature because it occurs in approximately 19% to 35% of affected family members (Table II) (1-3). In fact, more frequently clinical features of the MEN 2A syndrome include medullary thyroid carcinoma (MTC) and/or C-cell hyperplasia in almost all affected individuals, and pheochromocytoma in over 50% of patients. Therefore, it has been difficult to study the natural history of PHPT in MEN 2 because of its low incidence and the frequent late onset of clinical manifestations of hyperparathyroidism (4-6). Moreover, parathyroid disease is rarely the first feature recognized in MEN 2A, is generally mild and is sometimes expressed only as parathyroid tumors discovered incidentally in MTC surgery (7). Primary hyperparathyroidism in MEN 2A is a disease which is different from those observed in other hereditary neoplastic variants (i.e., MEN 1 and hyperparathyroidism-jaw tumor syndrome). In fact, the high rate of cure achieved with well-performed parathyroid surgery, as well as the low rate of persistence or recurrence of the disease, demonstrate that MEN 2A-related PHPT is a much less aggressive condition than is usually suggested (8).

Genetic aspects

RET proto-oncogene and hyperparathyroidism

Patients with primary hyperparathyroidism, either familial or sporadic, have one or more parathyroid glands enlarged: adenomas account for 80% of cases, hyperplasia for 15-20% and carcinomas for less than 1%. In the last few years, advances have been made in understanding the genetic event which underlies parathyroid tumorigenesis. The first step along this pathway was the demonstration of the monoclonality of these tumors: this has been observed in carcinomas, adenomas and even in parathyroid hyperplasia (9-11). This suggests the involvement of proto-oncogenes and tumor-suppressor genes in their pathogenesis; hence the increasing number of molecular genetic studies on this topic (11). In this setting, a lot of interest has been aroused by the MEN model, notably by MENIN, which acts as a tumor suppressor gene in MEN 1 and RET, which acts as proto-oncogene in MEN 2. Therefore, they have been studied as possible candidates for familial and non-familial hyperparathyroidism pathogenesis. While MENIN has been proved to be such an example, leading to the development of both familial and sporadic parathyroid tumors (11), the role of RET proto-oncogene is more controversial.

Table I - Hereditary disorders associated with primary hyperparathyroidism.

Hereditary disorders	Inheritance	Genes
Multiple endocrine neoplasia type 1	Autosomal dominant	*MENIN*
Multiple endocrine neoplasia type 2	Autosomal dominant	*RET*
Familial hypocalciuric hypercalcemia	Autosomal dominant	*CaSR*
Neonatal severe primary hyperparathyroidism	Autosomal dominant/recessive	*CaSR*
Hyperparathyroidism-jaw tumor syndrome	Autosomal dominant	*PARAFIBROMIN*
Familial isolated hyperparathyroidism	Autosomal dominant/recessive	†

† Potentially including all of the above mentioned disorders in occult forms.

Table II - Multiple endocrine neoplasia type 2 (MEN 2) syndromes.

Syndrome	Clinical features	Penetrance
Multiple endocrine neoplasia type 2A	Medullary thyroid carcinoma	100%
	Pheochromocytoma	50%
	Hyperparathyroidism	20%
MEN 2A variants		
– FMTC	Medullary thyroid carcinoma	100%
– MEN 2A/FMTC with Hirschsprung disease	MEN 2A or FMTC with Hirschsprung disease	
– MEN 2A with cutaneous lichen amyloidosis	MEN 2A with pruritic cutaneous lesions located over the upper back	
Multiple endocrine neoplasia type 2B	Medullary thyroid carcinoma	100%
	Pheochromocytoma	50%
	Marfanoid habitus	>90%
	Intestinal and mucosal ganglioneuromatosis	>90%

The RET gene, mapping to 10q11.2 (12), codes for a receptor tyrosine kinase which is expressed in the developing and adult neural ectoderm; its expression is critical for neural crest cell growth, migration, differentiation, survival and programmed cellular death (13, 14). RET sequence analysis of families with MEN 2 has demonstrated the presence of germ-line missense point mutations, leading to a gain of function in the tyrosine kinase activity and transforming RET into a dominantly acting oncogene (12). MEN 2 is a syndrome in which any affected tissues are likely to arise from neural crest, which supports the thesis that RET mutations may selectively provoke a neoplastic transformation in cell types with the same embryological origin and which expresses the proto-oncogene (15). In this regard, doubt has been thrown upon the pathogenetic role of RET in MEN 2 hyperparathyroidism, due to the endodermal origin of the parathyroid (16). Furthermore, in a prospective screening of MEN 2A patients who underwent early thyroidectomy, there was no evidence of parathyroid disease either at the time of surgery or after a mean follow-up of 10 years (17); thus, it has been supposed that the elevated calcitonin levels could be responsible for parathyroid tumorigenesis.

Now, the association of parathyroid disease with MEN 2A is regarded as being genetically determined. Several evidences support this hypothesis: the parathyroid cell precursors, which arise from the endoderm of the posterior branchial arches, express the RET proto-oncogene (13), confirming, therefore, its tissue-specific effect; indeed, RET expression has been demonstrated in normal parathyroid tissue, in sporadic and MEN 2A parathyroid tumors (18), as well the MEN 2A-related parathyroid tumors express the mutated RET gene (18); in contrast, patients with MEN 2B, despite high levels of calcitonin, do not develop hyperparathyroidism. Thus, in the above mentioned report (17), the missing evidence of hyperparathyroidism following early thyroidectomy is probably due to the loss of parathyroid glands or to a likely delayed onset of disease.

Because RET is also expressed in normal tissues (i.e., C-cells, adrenal medulla and parathyroids), it has been considered plausible that somatic mutations in the gene might contribute to the pathogenesis of the sporadic tumors. The transforming potential of the mutant RET proto-oncogene has been demonstrated in sporadic MTC and pheochromocytoma (19, 20); on the contrary, somatic RET mutations have not been found in sporadic parathyroid adenomas (18).

RET, hyperparathyroidism and genetic testing

A germ-line RET point mutation has been described in over 92% of MEN 2 families (21, 22). Therefore, DNA testing for RET mutations (23) has been proposed as a confirmative test in patients with a clinical suspicion of MEN 2 syndrome and as a predictive test in asymptomatic patients who are clinically at risk. The high sensitivity and specificity of the molecular test and its considerable impact in diagnosis and therapy have led to the introduction of RET testing in routine clinical practice (24).

By pooling a considerable amount of MEN 2 family data, a close relationship between genotype and phenotype has been

described (21, 25). MEN 2A has been associated with mutations in exon 10 (codons 609, 611, 618 and 620), exon 11 (codons 634, 635, 637), exon 13 (codons 790, 791), exon 14 (V804L) and exon 15 (codon 891); mutations at codon 634 are the most common in MEN 2A, accounting for 85% of cases (21, 26, 27).
Primary hyperparathyroidism occurs in about 20-30% of MEN 2A patients (28). Therefore, only some families develop the parathyroid disease; this suggests the existence of specific genotypes, expressing the hyperparathyroidism phenotype. The genotype-phenotype correlation studies in MEN 2 families show a significant association with codon 634 mutations; a relationship with codons 609, 611, 618, 620, 790 and 791 has been also described, although less frequently (21, 27, 28).
The most common alteration at codon 634 is a TGC to CGC (C634R) mutation, changing a cysteine to an arginine (21). The International RET Mutation Consortium Analysis showed a significant (P = 0.002) association between the C634R mutation and the development of hyperparathyroidism. The study pooled the data from different countries; this genotype-phenotype correlation was statistically significant only in the Cambridge dataset (21). If the latter is omitted from the Consortium dataset, the association is no longer significant (P = 0.22) (21). In a following study of 88 MEN 2A families harbouring the codon 634 mutation, no significant correlation with the familial risk of hyperparathyroidism has been found. In the same study an age-related and a mutation-specific penetrance of parathyroid disease has been demonstrated: particularly, the penetrance rose after 30 years and was significantly higher in C634R patients. It is remarkable that, despite the age-specific penetrance, the risk of hyperparathyroidism was significant below the age of 30, affecting 44% of patients. Thus, all codon 634 mutation carriers are at some risk of hyperparathyroidism and should be submitted to an early screening of the disease.

Clinical characteristics

Because of its hereditary nature, the clinical appearance of hyperparathyroidism in MEN 2A is rather early in risk subjects, around 35 years old, compared to the average 50 years old of the sporadic form; the onset age in the MEN 1 form is around 25-30 years old.
Often, an “incidental” parathyroid tumor is detected during thyroid removal for MTC.
From a clinical point of view, it is characterized by mild hypercalcaemia, that is mainly asymptomatic: only 15-25% of the subjects can be found with symptoms such as kidney stones or osteoporosis (28-32). In sporadic disease, the symptomatic forms account for 5-10% of the cases, while in MEN 1 patients the percentage rises above 50%. In a multicentric European retrospective study, in a sample of 67 subjects affected with PHPT MEN 2A related, 84% of the cases were found with asymptomatic hyperparathyroidism, while the remaining 16% were symptomatic (10 patients had kidney stones and one patient had bone disease) (28). Serum calcium was slightly higher in 69% of the subjects (less than 3 mmol l^{-1}), while in the normal range for 16% of them (28). Also, both MTC and hyperparathyroidism were diagnosed at the time of exploratory neck surgery in 75% of the sample, while for 4% and 18% the diagnosis of PHPT was available before or after surgery, respectively (28). Of note, patients in whom PHPT and MTC were diagnosed synchronously often had normal serum levels of calcium and parathyroid hormone (PTH) and the diagnosis of PHPT was based on morphology (enlargement of one or more glands) or histology (28). Thus, beyond the biological behaviour of parathyroid tumors, the earlier onset of MTC leading to an early diagnosis of PHPT and/or a strict clinical monitoring for the development of parathyroid disease might justify the large number of asymptomatic patients.
The hypercalcaemia recurrence rate after surgery reached 12% after 8 years (4), considering that in 42% of the subjects an adenectomy was carried out, in 31% a subtotal parathyroidectomy was done, and in 16% a parathyroidectomy with auto-transplantation of one of the gland was performed. It is be noted that the recurrence rate after subtotal parathyroidectomy is about 50% for MEN 1, 8-12 years after surgery (33).
The same results were obtained in two more studies from Cance, O’Riordain and colleagues, where the recovery rate after conservative surgery (removal of 1 or 2 glands in about half of the subjects) was 100%, with a recurrence rate of 3% (30, 34).
In conclusion, the hyperparathyroidism MEN 2A related is a clinical form less aggressive than commonly suggested, perhaps due to a misunderstanding of its relationship with MEN1, and does not differ from the sporadic type regarding its behaviour.

Management of PHPT in MEN 2A

Patients with MEN 2A should have annual screenings for hyperparathyroidism by serum calcium and intact PTH measurements. Parathyroidectomy should be considered in all patients with evidence of symptomatic disease. The objectives of parathyroid surgery are to a) obtain and maintain normocalcemia for the longest time possible, b) avoid iatrogenic hypoparathyroidism and c) facilitate future surgery for recurrent disease. Parathyroid surgery for familial PHPT continues to evolve as a result of improved preoperative imaging and the introduction of minimally invasive techniques, which includes intraoperative PTH assays. However, the high incidence of multiple gland disease, the possible enlargement of supernumerary glands, and a propensity for recurrent disease make MEN-related PHPT difficult to treat (7, 35, 36).

Diagnostic modalities

The sensitivity of preoperative Tc^{99m}-sestamibi and high-resolution ultrasound for glandular disease associated with primary hyperparathyroidism is presented in Table III. As shown, these techniques were less reliable in detecting multiple gland hyper-

Table III - Sensitivity of Tc^{99m}-sestamibi and high-resolution ultrasonography in primary hyperparathyroidism.

Diagnostic modalities	Sensitivity (%)
Tc^{99m}-sestamibi	
– Solitary adenomas	88.44
– Multiple gland hyperplasia	44.46
– Double adenomas	29.95
– Carcinomas	33
High resolution ultrasound	
– Solitary adenomas	78.55
– Multiple gland hyperplasia	34.86
– Double adenomas	16.2
– Carcinomas	100

plasia. Among all reported cases of hyperplastic gland disease, the sensitivity of sestamibi ranged from 0% to 100% with an overall mean sensitivity of 44.46%. Similarly, high-resolution ultrasonography has an overall sensitivity of 34.86% (37).

Surgical approaches

The rarity of MEN 2A-related PHPT has prevented the establishment of a well-defined therapeutical strategy, so that recommendations about the surgical approach have been controversial.
Some authors advocate total parathyroidectomy combined with autotransplantation of parathyroid tissue, generally to the forearm musculature. This approach results in about 5% of patients with permanent post-surgical hypoparathyroidism and 30% of patients with postoperative hypercalcemia. The latter could be easily managed with removal of transplanted tissue from the forearm with good results and little morbidity (35).
However, others favour subtotal parathyroidectomy such as the treatment of choice in order to decrease the risk of permanent hypoparathyroidism. This technique includes biopsy or subtotal resection of the most normal parathyroid gland followed by removal of the three most enlarged parathyroid glands. With this technique, persistent or recurrent hypercalcemia is reported in as many as 50% of patients with familial disease; however, hypercalcemia is probably due to the failure to remove a supernumerary gland, and not to the overgrowth of the small hyperplastic remnant. When any technique is performed, all removed parathyroid tissue must be confirmed by frozen section and then cryopreserved for future use if the patient should develop hypoparathyroidism (31).
Recently, a more conservative approach in MEN 2A-related PHPT has been suggested (38). This is mainly because the disease is much less aggressive than is usually expected and because a significant incidence (from 27% to 48%) of solitary adenoma has been reported. In fact, hypercalcemia is frequently mild and asymptomatic and the diagnosis is most often made synchronously or after thyroidectomy for MTC. At this time, generally, diagnosis of PHPT is based only on morphology (enlargement of one or more glands) or on histology (hyperplasia or adenoma of the parathyroid). Moreover, parathyroid disease seems to develop more rarely in patients who undergo a total thyroidectomy for early C-cell abnormalities. Probably, the inevitable loss of parathyroid tissue during total thyroidectomy decreases the incidence of parathyroid disease simply by reducing the number of parathyroid glands at risk. All these findings, together with the relatively low persistence or recurrence rate of PHPT, support the observations of less frequent multiple gland enlargement or supernumerary gland involvement. In fact, the two most important studies on patients undergoing surgical resection for MEN 2A-related PHPT demonstrate that, independently of the resection extent, about 90% of patients were cured. Hypercalcemia persisted in 3% and 11% of patients, respectively. During follow-up, hypercalcemia recurred in 12% and 9% of patients, independently to the resection extent. Interestingly, most of the failed primary operations and recurrences were due to insufficient exploration with an inability to recognize the presence of multiglandular disease at time of surgery (31, 36).
The overall observations seem to support the recommendations to adopt a conservative attitude toward parathyroid surgery, rather than a systematic total or subtotal resection. Therefore, surgical management should focus on the preservation of parathyroid function. During the operation, all four parathyroid glands should be identified and a careful search for supernumerary glands should be performed. Only the macroscopically enlarged glands should be removed. This technique is associated with low rate of persistent or recurrent PHPT and it offers a better chance of avoiding postoperative hypoparathyroidism. It may be wise to concomitantly undertake cervical thymectomy. If all parathyroid glands are enlarged, the least enlarged gland or the least enlarged portion of one gland should be preserved. Patients should have catecholamine and metabolite measurements to rule out a diagnosis of pheochromocitoma before neck exploration for parathyroidectomy.
Surgery is the only effective long-term therapy for primary hyperparathyroidism. Pharmacologic therapy is necessary when patients have a hypercalcemic crisis, but this is unusual for patients with MEN 2A. The goals of medical therapy are intravenous normal saline hydration (2-8 L/day) and diuresis, after adequate intravenous hydration with furosemide. There are several agents that are effective for transiently reducing the serum calcium level, until a neck exploration and parathyroidectomy can be performed. These agents inhibit bone resorption and include bisphosphonates and calcitonin.
Finally, most of the patients with MEN 2A-related PHPT have mild disease and they could be classified as asymptomatic based on the NIH consensus conference regarding the diagnosis and management of asymptomatic PHPT. Therefore, these patients can be followed up safely without parathyroid surgery (39).

The role of minimally invasive parathyroidectomy (MIP) in MEN 2A-related PHPT

The MIP technique has become the standard of care for sporadic PHPT in institutions with significant experience in this procedure. In PHPT associated with MEN 2A, where uniglandular uptake is noted on preoperative imaging, MIP may be considered. Although it is likely that persistence and recurrence rates will be higher compared with the conventional cervical exploration, MIP has the advantage of causing minimal tissue trauma and thus facilitating reoperations. Moreover, MIP may have a role in recurrent disease, when preoperative imaging suggests a single focus. However, the role of intraoperative PTH measurement to guide the resection extent is still debated, because of the significant risk of false-positive rate in patients with multiglandular disease (up to 50%). To reduce this risk, it has been suggested that a decline in PTH serum level > 80% (not > 50%) is necessary to accept adequate excision of parathyroid tissue (40).

Conclusion

It is difficult to study the natural history of hyperparathyroidism in MEN 2A, because of its low incidence (5-20%) and the frequent late onset of clinical features of hyperparathyroidism compared to MEN 1.
Nonetheless, looking at the very few data available in the literature, three interesting points emerged: firstly, the examination of pedigrees suggests that PHPT clusters in some families, whereas other MEN 2A families might not express the trait, a fact which suggests a sort of phenotype-genotype correlation; secondly, PHPT in MEN 2A is mild and asymptomatic; thirdly, there is a relatively low recurrence rate of PHPT after surgery. These findings suggest a conservative approach in the surgical management of MEN 2A-related PHPT.

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